

Appl. No. 09/979,593
Reply dated November 3, 2003
Reply to Office action mailed October 1, 2003

Amendments to the Claims

This listing of claims will replace the prior version of claims in the application:

Listing of Claims:

1. (original) A method for haplotyping the Intercellular Adhesion Molecule 2 (ICAM2) gene of an individual which comprises determining whether the individual has one of the ICAM2 haplotypes shown in Table 5 or one of the haplotype pairs shown in Table 4, wherein each of the haplotypes in Table 5 comprises the corresponding set of SEQ ID NOS shown in Table 6.
2. (original) The method of claim 1, wherein the determining step comprises identifying the phased sequence of nucleotides present at each of polymorphic sites (PS) PS1-12 on at least one copy of the individual's ICAM2 gene, wherein PS1-12 have the location and alternative alleles shown in SEQ ID NO:59 (Fig. 1).
3. (original) The method of claim 1, wherein the determining step comprises identifying the phased sequence of nucleotides present at each of PS1-12 on both copies of the individual's ICAM2 gene.
4. (original) A method for genotyping the Intercellular Adhesion Molecule 2 (ICAM2) gene of an individual, comprising determining for the two copies of the ICAM2 gene present in the individual the identity of the nucleotide pair at one or more polymorphic sites (PS) selected from the group consisting of PS1, PS2, PS3, PS4, PS5, PS6, PS7, PS8, PS9, PS10, and PS11, wherein the one or more PS have the location and alternative alleles shown in SEQ ID NO:59 (Fig. 1).
5. (original) The method of claim 4, wherein the determining step comprises:
 - (a) isolating from the individual a nucleic acid mixture comprising both copies of the ICAM2 gene, or a fragment thereof, that are present in the individual;
 - (b) amplifying from the nucleic acid mixture a target region containing the selected polymorphic site;
 - (c) hybridizing a primer extension oligonucleotide to one allele of the amplified target region;
 - (d) performing a nucleic acid template-dependent, primer extension reaction on the

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- hybridized genotyping oligonucleotide in the presence of at least two different terminators of the reaction, wherein said terminators are complementary to the alternative nucleotides present at the selected polymorphic site; and
- (e) detecting the presence and identity of the terminator in the extended genotyping oligonucleotide.
6. (original) The method of claim 4, which comprises determining for the two copies of the ICAM2 gene present in the individual the identity of the nucleotide pair at each of PS1-12.
7. (original) A method for haplotyping the Intercellular Adhesion Molecule 2 (ICAM2) gene of an individual which comprises determining, for one copy of the ICAM2 gene present in the individual, the identity of the nucleotide at two or more polymorphic sites (PS) selected from the group consisting of PS1, PS2, PS3, PS4, PS5, PS6, PS7, PS8, PS9, PS10, and PS11, wherein the two or more PS have the location and alternative alleles shown in SEQ ID NO:59 (Fig.1).
8. (original) The method of claim 7, further comprising determining the identity of the nucleotide at PS12, which has the location and alternative alleles shown in SEQ ID NO:59 (Fig. 1).
9. (original) The method of claim 7, wherein the determining step comprises:
- (a) isolating from the individual a nucleic acid sample containing only one of the two copies of the ICAM2 gene, or a fragment thereof, that is present in the individual;
 - (b) amplifying from the nucleic acid molecule a target region containing the selected polymorphic site;
 - (c) hybridizing a primer extension oligonucleotide to one allele of the amplified target region;
 - (d) performing a nucleic acid template-dependent, primer extension reaction on the hybridized genotyping oligonucleotide in the presence of at least two different terminators of the reaction, wherein said terminators are complementary to the alternative nucleotides present at the selected polymorphic site; and

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- (e) detecting the presence and identity of the terminator in the extended genotyping oligonucleotide.
10. (original) A method for predicting a haplotype pair for the Intercellular Adhesion Molecule 2 (ICAM2) gene of an individual comprising:
- (a) identifying an ICAM2 genotype for the individual, wherein the genotype comprises the nucleotide pair at two or more polymorphic sites (PS) selected from the group consisting of PS1, PS2, PS3, PS4, PS5, PS6, PS7, PS8, PS9, PS10, and PS11, having the location and alternative alleles shown in SEQ ID NO:59 (Fig.1);
 - (b) enumerating all possible haplotype pairs which are consistent with the genotype;
 - (c) comparing the possible haplotype pairs to the data in Table 4; and
 - (d) assigning a haplotype pair to the individual that is consistent with the data.
11. (original) The method of claim 10, wherein the identified genotype of the individual comprises the nucleotide pair at each of PS1-12, which have the location and alternative alleles shown in SEQ ID NO:59 (Fig. 1).
12. (original) A method for identifying an association between a trait and at least one haplotype or haplotype pair of the Intercellular Adhesion Molecule 2 (ICAM2) gene which comprises comparing the frequency of the haplotype or haplotype pair in a population exhibiting the trait with the frequency of the haplotype or haplotype pair in a reference population, wherein the haplotype is selected from haplotypes 1-14 shown in Table 5, wherein each of the haplotypes in Table 5 comprises the corresponding set of SEQ ID NOS shown in Table 6, and the haplotype pair is selected from the haplotype pairs shown in Table 4, wherein a higher frequency of the haplotype or haplotype pair in the trait population than in the reference population indicates the trait is associated with the haplotype or haplotype pair.
13. (original) The method of claim 12, wherein the trait is a clinical response to a drug targeting ICAM2.
14. (original) A composition comprising at least one genotyping oligonucleotide for detecting a polymorphism in the Intercellular Adhesion Molecule 2 (ICAM2) gene at a polymorphic site (PS) selected from the group consisting of PS1, PS2, PS3, PS4, PS5, PS6, PS7, PS8, PS9,

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PS10, and PS11, having the location and alternative alleles shown in SEQ ID NO:59 (Fig.1).

15. (original) The composition of claim 14, wherein the genotyping oligonucleotide is an allele-specific oligonucleotide that specifically hybridizes to an allele of the ICAM2 gene at a region containing the polymorphic site.
16. (original) The composition of claim 15, wherein the allele-specific oligonucleotide comprises a nucleotide sequence selected from the group consisting of SEQ ID NOS:4-14, the complements of SEQ ID NOS:4-14, and SEQ ID NOS:15-36.
17. (original) The composition of claim 14, wherein the genotyping oligonucleotide is a primer-extension oligonucleotide.
18. (original) The composition of claim 17, wherein the primer extension oligonucleotide comprises a nucleotide sequence selected from the group consisting of SEQ ID NOS:37-58.
19. (original) A kit for genotyping the ICAM2 gene of an individual, which comprises a set of oligonucleotides designed to genotype each of polymorphic sites (PS) PS1, PS2, PS3, PS4, PS5, PS6, PS7, PS8, PS9, PS10, and PS11, having the location and alternative alleles shown in SEQ ID NO:59 (Fig.1).
20. (original) The kit of claim 19, which further comprises oligonucleotides designed to genotype PS12.
21. (currently amended) An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of:
 - (a) a first nucleotide sequence which is a polymorphic variant of a reference sequence for the Intercellular Adhesion Molecule 2 (ICAM2) gene or a fragment thereof, wherein the reference sequence comprises SEQ ID NO:1 and the polymorphic variant comprises an ICAM2 isogene defined by a haplotype selected from the group consisting of haplotypes 1-2, 4-14 in Table 5, wherein the isogene comprises SEQ ID

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NO:59, except where substituted by the sequence of alleles for the correspondingly numbered haplotype at the polymorphic sites whose nucleotide positions are shown in SEQ ID NO:59 wherein each of the haplotypes in Table 5 comprises the corresponding set of SEQ ID NOS shown in Table 6, and the fragment comprises at least one novel nucleotide at a polymorphic site (PS) selected from the group consisting of guanine at PS1, thymine at PS2, guanine at PS3, cytosine at PS4, guanine at PS5, adenine at PS6, guanine at PS7, guanine at PS8, adenine at PS9, adenine at PS10, and adenine at PS11, wherein each polymorphic site has the position shown in SEQ ID NO:59; and

(b) a second nucleotide sequence which is complementary to the first nucleotide sequence.

22.(original) The isolated polynucleotide of claim 21, which is a DNA molecule and comprises both the first and second nucleotide sequences and further comprises expression regulatory elements operably linked to the first nucleotide sequence.

23.(original) A recombinant nonhuman organism transformed or transfected with the isolated polynucleotide of claim 21, wherein the organism expresses an ICAM2 protein encoded by the first nucleotide sequence.

24.(original) The recombinant organism of claim 23, which is a nonhuman transgenic animal.

25. (original) The isolated polynucleotide of claim 21, wherein the first nucleotide sequence is a polymorphic variant of a fragment of the ICAM2 gene, the fragment comprising one or more polymorphic sites (PS) with the polymorphic allele selected from the group consisting of guanine at PS1, thymine at PS2, guanine at PS3, cytosine at PS4, guanine at PS5, adenine at PS6, guanine at PS7, guanine at PS8, adenine at PS9, adenine at PS10, and adenine at PS11.

26.(currently amended) An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of:

(a) a first nucleotide sequence which comprises an ICAM2 coding sequence encoding a human ICAM2 polypeptide, wherein the coding sequence is selected from the group consisting of ICAM2 coding sequences A, B, C, D, E, and F represented in the table below, wherein the selected coding

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sequence comprises SEQ ID NO:2, except where substituted by the corresponding sequence of alleles for the selected coding sequence at the set of polymorphic sites presented in the table below.

Region	PS	PS	Coding Sequence Variants(d)					
Examined(a)	No.(b)	Position(c)	A	B	C	D	E	F
1-828	2	12	C	C	T	C	C	C
1-828	3	43	A	A	A	A	A	G
1-828	9	660	A	G	G	G	G	G
1-828	10	687	G	G	G	A	G	G
1-828	11	746	G	G	G	G	A	G
1-828	12	822	G	A	G	G	G	G

(a) Region examined represents the nucleotide positions in SEQ ID NO:2 defining the start and stop positions of the regions sequenced; (b) PS = polymorphic site; (c) Position of PS within SEQ ID NO:2; (d) Alleles for ITGB3 coding sequences are presented 5' to 3' in each column. The letter at the top of each column designates the the coding sequence variant.

and

(b) a second nucleotide sequence which is complementary to the first nucleotide sequence.

~~which is a polymorphic variant of a reference sequence for the ICAM2 coding sequence or a fragment thereof, wherein the reference sequence comprises SEQ ID NO:2 and the polymorphic variant comprises a set of oligonucleotides selected from the group consisting of the corresponding sets of SEQ ID NOS shown in Table 7.~~

27.(original) A recombinant nonhuman organism transformed or transfected with the isolated polynucleotide of claim 26, wherein the organism expresses a Intercellular Adhesion Molecule 2 (ICAM2) protein encoded by the polymorphic variant sequence.

28.(original) The recombinant organism of claim 27, which is a nonhuman transgenic animal.

29. (currently amended) An isolated polypeptide comprising an amino acid sequence which is a polymorphic variant of a reference sequence for the ICAM2 protein or a fragment thereof, wherein the reference sequence comprises SEQ ID NO:3 and the polymorphic variant is encoded by a polymorphic variant of the ICAM2 coding sequence which comprises alanine at a position corresponding to 15 or aspartate at a position corresponding to 249. ~~a set of oligonucleotides selected from the group consisting of the sets of SEQ ID~~

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~~NOS shown in Table 7.~~

30. (original) An isolated antibody specific for and immunoreactive with the isolated polypeptide of claim 29.
31. (original) A method for screening for drugs targeting the isolated polypeptide of claim 29 which comprises contacting the ICAM2 polymorphic variant with a candidate agent and assaying for binding activity.
32. (canceled)
33. (currently amended) A genome anthology for the Intercellular Adhesion Molecule 2 (ICAM2) gene which comprises two or more ICAM2 isogenes defined by any one of haplotypes 1-14 shown in Table 5, wherein each of the haplotypes in Table 5 ~~comprises~~ isogene comprises SEQ ID NO:59, except where substituted by the sequence of alleles for the correspondingly numbered haplotype at the polymorphic sites whose nucleotide positions are shown in SEQ ID NO:59, and wherein at least one of the ICAM2 isogenes is defined by any one of haplotypes 1-2, 4-14, the corresponding set of SEQ ID NOS shown in Table 6.